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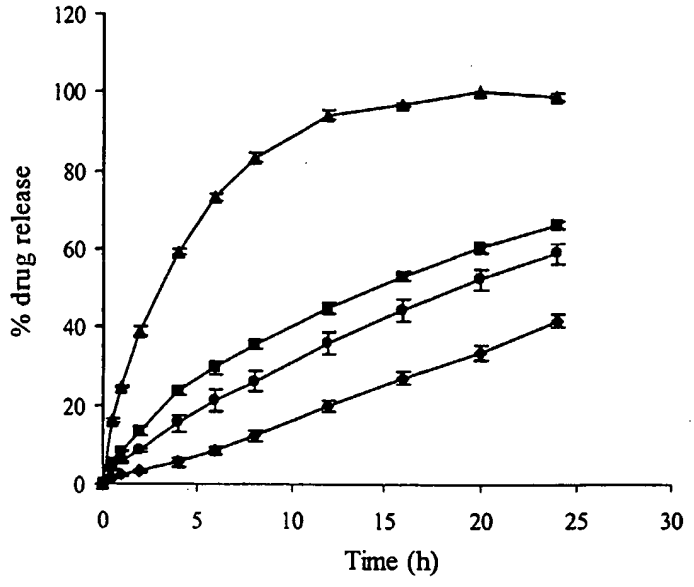
(54) Title: COMPOSITE SOLID SHAPED ARTICLES FOR THE CONTROLLED DELIVERY OF BIOLOGICALLY ACTIVE INGREDIENTS



(57) Abstract: A biologically active composite solid shaped article comprising: (a) an outer layer comprising: at least one layer component selected from a starch component, a cellulose derivative and an acrylate (co)polymer, and optionally one or more additives, and further optionally at least a biologically active ingredient A, and (b) an inner core filling the said outer layer and comprising: at least a biologically active ingredient B, at least one core component selected from a starch component, a lipophilic material, a cellulose derivative and an acrylate (co)polymer, and optionally one or more additives. The main biologically inactive components of the outer layer and of the inner core are selected in order to withstand diffusion of water and water-based body fluids into the core while providing controlled release of the biologically active ingredients(s).

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80°C from powder feeder to die. The extrudates were manually cut into pieces of 10 cm and dried for 48 hours at 60°C prior to analysis. Dissolution was performed in 6-fold on extrudate pieces of approximately 3 cm. The dissolution system consisted of a VK 7000 dissolution bath and a VK 8000 automatic sampling station (commercially available from VanKel, USA). The paddle method (Eur. Ph.) at 100 rpm and 37 ± 0.5°C was selected using water as the dissolution medium. Samples were taken at 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 hours respectively and analyzed by spectrophotometry after appropriate dilution. The resulting dissolution profile is shown in figure 1. Due to the promising release profile *in vitro* (80% drug released in 8 hours), the formulation was also evaluated *in vivo* in a crossover randomized study on 8 healthy human volunteers aged between 20 and 27 years. The obtained plasma profiles are presented in figure 2, from which it is obvious that only a slight to intermediate sustained release effect is obtained with this hot stage extrusion formulation. Therefore it was the objective of further research to investigate if the drug release could be affected by changes in formulation composition or process parameters in order to achieve high efficacy and high quality starch based hot stage extruded matrices with a slower *in vitro* drug release profile than the formulation that was tested *in vivo* according to the above publication.

The conclusions of the research work published by D. Henrist et al. in *Int. J. Pharm.* (1999) 188, 111-119 and *Int. J. Pharm.* (1999) 189, 7-17 on the formulation composition and the process parameters can be summarized as follows:

1) the system seems to be very robust, meaning that it is difficult to significantly modify the *in vitro* drug release profiles,
2) all profiles exhibit a burst release effect which is difficult to control, and
3) it is highly improbable that the *in vivo* behaviour of the extruded matrix can be altered through changes in formulation composition or process parameters.

Further, controlled release pharmaceutical compositions including acrylic polymers are also well known. For instance, EP-A-544,144 discloses a rigid pharmaceutical retard form obtained by melt-extruding at 50-200°C and

continuously shaping a mixture of a pharmaceutical substance with a polymer melt having the following composition:

(a) at least 6% by weight, based on the entire retard form, of at least a water-insoluble poly(meth)acrylate with a Tg from –60°C to 180°C,

(b) a water-insoluble hydroxyalkyl(methyl)cellulose with 2 or 3 carbon atoms in the hydroxyalkyl rest, and/or a N-vinylpyrrolidone polymer with up to 50% by weight vinyl acetate,

in a ratio (a):(b) from 5:95 to 95:5, and

(c) one or more pharmaceutical aids.

Controlled release pharmaceutical compositions based on polyglycols are also well known. For instance, International Patent Application published WO 89/09066 discloses a controlled-delivery composition comprising:

(a) a water-soluble crystalline polymer matrix,

(b) a surface-active agent with a melting point lower than that of polymer (a), dispersed in polymer (a) in an amount of 0-50% by weight of (a) + (b), and having a substantially hydrophilic domain compatible with (i.e. emulsifiable in) polymer (a) and another substantially lipophilic domain, and

(c) an active substance substantially homogeneously dispersed in polymer (a), wherein the agent (b) and/or the substance (c) reduce the water affinity of domains between grains and in cracks in polymer (a), thereby substantially eliminating water diffusion at the interface between polymer crystals, so that controlled delivery is predominantly effected by the dissolving action of an aqueous medium on the surface of the composition. The composition may optionally include a filler such as dextrin. The composition may have the shape of a cylindrical rod provided with a coating opened at one or both ends (in which case it may be produced by co-extruding of the matrix material with the active substance dispersed therein and the coating), or the shape of a hollow cylinder (in which case it may be produced by extrusion, compression molding or injection molding). More specifically, the surface-active agent (b) is a non-ionic emulsifier such as polyethylene glycol monostearate and the crystalline polymer matrix (a) is a polyglycol.

International Patent Application published WO 95/22962 discloses a controlled-delivery composition comprising:

(a) a matrix comprising an active substance and being erodible in an aqueous medium, and

(b) a coating having at least one opening exposing at least one surface of said matrix and comprising (i) a thermoplastic, water-insoluble first cellulose derivative and (ii) at least one of a plasticizer (e.g. a non-ionic surfactant), a filler and/or a second cellulose derivative, said coating being erodible, upon exposure to an aqueous medium, at a rate not above the erosion rate of the matrix.

More specifically, the said first cellulose derivative is an extrudable cellulose ether, the matrix is a polyethyleneglycol or a thermoplastic, water-insoluble cellulose derivative such as (i), and the filler may be starch.

International Patent Application published WO 99/51208 discloses a controlled-delivery composition comprising a matrix being erodible in an aqueous medium and allowing no diffusion of water into the composition beyond any exposed surface layer of the matrix, comprising a water soluble crystalline polymer (polyethylene glycol) with a water-dispersible (non-ionic) surface active agent dispersed therein, an active substance and further comprising a release modifier that regulates erosion of the matrix within a pH range of 2 to 7.

The common goal of the three previously cited patent documents is to overcome the drawbacks of existing sustained release compositions, namely (i) the active substance concentration is not kept constant in plasma for the entire period when the dosage form is present in the body, and (ii) penetration of water through the coating may cause hydrolysis of active substances which are unstable in an aqueous environment. All three documents consider as an essential feature to prevent the ingress of water and water-based body fluids into the composition and thus to prevent contact between the active substance and aqueous liquid except at the eroding surface.

Example 1 of International Patent Application published WO 99/51208 discloses a controlled release matrix composition comprising 40% polyethylene glycol and 46% potato starch which is said not to meet the 4 hours erosion time requirement of the dissolution test method disclosed in USP 23, NF 18 (the United States Pharmacopeia, 1995) at an acidic pH of 2.0 and

agitation at 150 rpm, whereas corresponding examples not including starch by far met such requirement. Therefore, alike from the conclusions drawn by D. Henrist et al. (see figure 2) in the scientific publications referred above, the skilled person was not motivated to consider starch as a main component of a sustained release composition.

Therefore a need in the art remains for hot stage extruded drug/matrix systems, in particular for such systems based on a low cost material alike starch, capable of exhibiting a marked drug sustained release effect without burst release effect. A need also exists in the art for a controlled release pharmaceutical composition comprising a core and a coating, which composition is (contrary to the teaching of the three above-cited International Patent Applications) able to withstand, i.e. allow, diffusion of water and water-based body fluids into the core. These are some of the technical problems to be solved by the present invention.

SUMMARY OF THE INVENTION

A new approach to these problems is based on a "double matrix" system comprising or consisting of an outer layer, for instance in the form of a pipe or tube (such as hereinafter defined), and an inner core fitted into and/or filling the said outer layer, wherein the main biologically inactive components of the outer layer and of the inner core are suitably selected in order to allow diffusion of water and water-based body fluids into the core while simultaneously being able to provide controlled release of a biologically active (agronomical or pharmaceutical) ingredient included in the system.

Thus, in a first embodiment, the present invention provides a biologically active composite solid shaped article comprising:

a) an outer layer comprising:
   - at least a layer component selected from a starch component, a cellulose derivative and an acrylate (co)polymer, and
   - optionally one or more additives selected from plasticizers for the said layer component, lubricants, rate controlling polymers and other excipients, and
   - further optionally at least a biologically active ingredient A, and

b) an inner core filling or fitted into the said outer layer and comprising:

- at least a biologically active ingredient B,
- at least one core component selected from a starch component, a lipophilic material, a cellulose derivative and an acrylate (co)polymer, and
- optionally one or more additives selected from plasticizers for the said core component, lubricants, rate controlling polymers and other excipients.

In a second embodiment, the present invention provides a first process for making a biologically active composite solid shaped article, comprising:

(a) forming a mixture (A) comprising:

- at least one layer component selected from a starch component, a cellulose derivative and an acrylate (co)polymer, and
- optionally one or more additives selected from plasticizers for the said layer component, lubricants, rate controlling polymers and other excipients, and
- further optionally a biologically active ingredient A,

(b) forming a mixture (B) comprising:

- at least a biologically active ingredient B,
- at least one core component selected from a starch component, a cellulose derivative and an acrylate (co)polymer, and
- optionally one or more additives selected from plasticizers for the said core component, lubricants, rate controlling polymers and other excipients, and

(c) co-extruding mixture (A) and mixture (B) at a temperature from about 20 to 180°C in order to form an outer layer from the extrudate of mixture (A) and an inner core filling the said outer layer from the extrudate of mixture (B).

An alternative process for making a biologically active composite solid shaped article comprises separately extruding mixture (A) and mixture (B), as herein-above defined in the first process, at a temperature from about 20 to 180°C in order to form an outer layer from the extrudate of mixture (A) and an inner core from the extrudate of mixture (B) and further assembling, manually or automatically, both extrudates in such a manner that the inner core fills the outer layer.

Another alternative process for making a biologically active composite solid shaped article according to this invention, when the core component consists of a lipophilic material, comprises:

(a) forming a mixture (A), as herein-above defined in the first process, and extruding said mixture at a temperature from about 20 to 180°C in order to form an outer layer from the extrudate of mixture (A),

(b) forming a mixture (C) comprising:

- at least a biologically active ingredient B,
- a lipophilic material as a core component, and
- optionally one or more additives selected from plasticizers for the said core component, lubricants, rate controlling polymers and other excipients, and

(c) melt-homogenizing mixture (C) and filling the melt-homogenized mixture (C)

into the outer layer during or after extrusion of mixture (A).

Yet alternative methods for making a composite solid shaped article according to this invention are known in the art and include, for instance, fluidized bed coating.

Thirdly the present invention provides a biologically active product or formulation, such as a tablet or gelule, comprising a composite solid shaped article as described herein-above or obtainable from any process as described herein-above, which can be used for the controlled, e.g. sustained, delivery of biologically active ingredients for agronomic, prophylactic and/or therapeutic (i.e. both pharmaceutical in humans and veterinary in animals) applications, e.g. as a medicament.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the *in vitro* release profile of a hot stage extruded formulation consisting of 53 % corn starch, 15% sorbitol, 30% theophylline monohydrate and 2% glyceryl monostearate.

Figure 2 shows individual (—) and mean ( ) plasma concentration-time profiles after administration of 300 mg theophylline as a hot stage extrusion formulation consisting of 53% corn starch, 15% sorbitol, 30% theophylline monohydrate and 2 % glyceryl monostearate to 8 healthy volunteers.

Figure 3 shows dissolution profiles of three different composite solid shaped articles according to the invention, compared with a reference hot stage extruded formulation of the prior art.

Figure 4 shows dissolution profiles of composite solid shaped articles according to the invention, having different inner core diameters, compared with a reference hot stage extruded formulation of the prior art.

Figure 5 shows dissolution profiles of composite solid shaped articles according to the invention, having different drug loading in the inner core.

Figure 6 shows dissolution profiles of composite solid shaped articles according to the invention, having different drug loading in the inner core.

Figure 7 shows the mean plasma concentration-time *in vivo* profiles after administration of composite solid shaped articles according to the invention, compared with the single matrix system of the prior art.

Figure 8 is a schematic representation of a product in accordance with an embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention will be described with reference to certain embodiments and figures but is not limited thereto but only by the attached claims.

More specifically this invention provides a biologically active composite solid shaped article comprising:

(a) an outer layer comprising, per 100 parts by weight of the said layer:

- from 1 to 100 parts of at least one layer component selected from a starch component, a cellulose derivative or an acrylate (co)polymer,

- from 0 to 50 parts of one or more plasticizers for the said layer component,
- from 0 to 50 parts of one or more lubricants,
- from 0 to 50 parts of one or more rate controlling polymers,
- from 0 to 50 parts of one or more other excipients, and
- from 0 to 99 parts of at least a biologically active ingredient A, and

(b) an inner core filling the said outer layer and comprising, per 100 parts by weight of the said core:

- from 1 to 100 parts of at least one core component selected from a starch component, a lipophilic material, a cellulose derivative or an acrylate (co)polymer,
- from 0 to 50 parts of one or more plasticizers for the said core component,
- from 0 to 50 parts of one or more lubricants,
- from 0 to 50 parts of one or more rate controlling polymers,
- from 0 to 50 parts of one or more other excipients, and
- from 0 to 99 parts of at least a biologically active ingredient B.

Preferably the core component of the biologically active composite solid shaped article comprises the major part of the whole biologically active ingredient dose, whereas the layer component optionally contains only a minor part of the said dose in order to prevent a lag phase in the dissolution profile. The biologically active ingredient(s) B present in the inner core may be different from or the same as the biologically active ingredient(s) A present in the outer layer of the composite solid shaped article of this invention, thereby opening opportunities for therapeutically synergistic combinations of active ingredients or for separating incompatible drugs.

A schematic representation of a product according to the present invention is shown in figure 8 showing an outer cylindrical layer and an inner core which fills the outer layer. .

For a better understanding of the scope of this invention, the following definitions are provided:

- the term " starch component " as used herein refers to any polymaltoside or poly-α 1,4-glucoside and to any chemically or

physically modified form thereof. Poly-α 1,4-glucosides include leguminous, cereal or tuber starches or a hydrolysate of such a starch. A non-limiting list of starch sources includes corn, wheat, barley, oats, pea, waxy maize, arrowroot, sorghum, rice, waxy sorghum, waxy rice, soya, potato. Further the poly-α 1,4-glucoside may include branched or unbranched polymaltoses such as amylopectin or amylose or thinned starches (hydrolysates of starch) including maltodextrose. Modified starches include grafted starches obtained for instance by grafting at least an acrylic monomer such as acrylic acid, methyl acrylate, acrylonitrile and the like onto starch, and which may be further at least partially saponified.

- The term " cellulose derivative" as used herein refers to e.g. ethylcellulose, methylcellulose, ethylmethylcellulose, ethylhydroxyethylcellulose, hydroxyethylcellulose, hydroxyethylmethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose phtalate, hydroxymethylcellulose, hydroxymethylpropylcellulose, and similar cellulose compounds which, when used as the main biologically inactive component of the outer layer and/or the inner core of the composite article of the invention, are able to withstand diffusion of water and water-based body fluids into the core while providing controlled release properties to the composite article.
- The term " acrylate (co)polymer " as used herein refers to homopolymers and copolymers of at least one C_{1-10}alkyl or C_{1-10}alkylamino acrylate or methacrylate, further optionally containing a minor amount (up to about 10%) of a hydrophilic acrylic monomer such as acrylic or methacrylic acid. Non-limiting examples are polyethylacrylate, polymethylmethacrylate and the like.
- The term " lipophilic material " as used herein refers for instance to triglycerides such as tripalmitine, distearylpalmitine and the like, but also to mono- and diglycerides, polyglycolysed glycerides, fatty acid esters,

tocopherol derivatives (such as tocopherol polyethylene glycol succinate), and mixtures thereof.

- The term "biologically active ingredient " as used herein refers to therapeutic, diagnostic and prophylactic agents as well as other agents, e.g. selected from insecticides, pesticides, herbicides, plant growth regulators, fertilizers, anti-microbial agents (in particular fungicides and bactericides), admissible for use in plants, animals and humans. The therapeutic agent can be selected for its specific properties such as for instance its anti-thrombotic, anti-inflammatory, anti-proliferative or anti-microbial efficiency. The latter include for instance anti-microbial agents such as broad spectrum antibiotics for combating clinical and sub-clinical infection, for example gentamycin, vancomycine and the like. Other suitable therapeutic agents are naturally occurring or synthetic organic or inorganic compounds well known in the art, including non-steroidal anti-inflammatory drugs, proteins and peptides (produced either by isolation from natural sources or recombinantly), hormones, bone repair promoters, carbohydrates, antineoplastic agents, antiangiogenic agents, vasoactive agents, anticoagulants, immunomodulators, cytotoxic agents, antiviral agents, antibodies, neurotransmitters, oligonucleotides, lipids, plasmids, DNA and the like. Suitable therapeutically active proteins include e.g. fibroblast growth factors, epidermal growth factors, platelet-derived growth factors, macrophage-derived growth factors such as granulocyte macrophage colony stimulating factors, ciliary neurotrophic factors, tissue plasminogen activator, B cell stimulating factors, cartilage induction factor, differentiating factors, growth hormone releasing factors, human growth hormone, hepatocyte growth factors, immunoglobulins, insulin-like growth factors, interleukins, cytokines, interferons, tumor necrosis factors, nerve growth factors, endothelial growth factors, osteogenic factor extract, T cell growth factors, tumor growth inhibitors, enzymes and the like, as well as fragments thereof. Suitable diagnostic agents include conventional imaging agents (for instance as used in tomography, fluoroscopy, magnetic resonance imaging and the like)

such as transition metal chelates. Suitable anti-microbial agents include e.g. halogenated phenols, chlorinated diphenylethers, aldehydes, alcohols such as phenoxyethanol, carboxylic acids and their derivatives, organometallic compounds such as tributyltin compounds, iodine compounds, mono- and polyamines, sulfonium and phosphonium compounds; mercapto compounds as well as their alkaline, alkaline-earth and heavy metal salts; ureas such as trihalocarbanilide, isothia- and benzisothiazolone derivatives. Suitable insecticides include natural ones, e.g. nicotine, rotenone, pyrethrum and the like, and synthetic ones like chlorinated hydrocarbons, organophosphorus compounds, biological insecticides (e.g. products derived from *Bacillus thuringiensis*), synthetic pyrethroids, organosilicon compounds, nitro-imines and nitromethylenes. Suitable fungicides include e.g. dithiocarbamates, nitrophenol derivatives, heterocyclic compounds (including thiophtalimides, imidazoles, triazines, thiadiazoles, triazoles and the like), acylalanines, phenylbenzamides and tin compounds. Suitable herbicides include e.g. trichloroacetic and aromatic carboxylic acids and their salts, substituted ureas and triazines, diphenyl ether derivatives, anilides, uraciles, nitriles and the like. Suitable fertilizers include e.g. ammonium sulphate, ammonium nitrate, ammonium phosphate and the like, and mixtures thereof.

- The term " plasticizer " as used herein refers to compounds such as glycerol, polyols (namely tetraols, pentols and hexols such as sorbitol), esters formed between glycerol and acetic acid (e.g. triacetine), sugars, glycol glycoside, poly(ethylene glycol), fatty acids and esters thereof with polyethylene glycol, propylene glycol, butylene glycol, phtalate esters, sebacate esters and the like. The nature of the specific plasticizer to be used will vary, in a manner well known to those skilled in the art, depending on the layer component or core component to be plasticized.
- The term " lubricant " as used herein refers to compounds such as fatty acids, mono- and diglycerides, phosphoaminolipids such as lecithine and synthetic phospholipids of the cephalin or lecithin type such as

phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerine, lysolecithin, cardiolipin, dioctanylphosphatidyl-choline, dipalmitoylphoshati- dylcholine and their mixtures, water-soluble soaps and water-soluble synthetic surface-active agents. Suitable soaps are alkaline or alkaline-earth metal salts, unsubstituted or substituted ammonium salts of higher fatty acids (C_{10}-C_{22}), e.g. the sodium or potassium salts of oleic or stearic acid, or of natural fatty acid mixtures obtainable form coconut oil or tallow oil. Synthetic surface-active agents (surfactants) include anionic, cationic and non-ionic surfactants, e.g. sodium or calcium salts of polyacrylic acid; sulphonated benzimidazole derivatives preferably containing 8 to 22 carbon atoms; alkylarylsulphonates; and fatty sulphonates or sulphates, usually in the form of alkaline or alkaline-earth metal salts, unsubstituted ammonium salts or ammonium salts substituted with an alkyl or acyl radical having from 8 to 22 carbon atoms, e.g. the sodium or calcium salt of lignosulphonic acid or dodecylsulphonic acid or a mixture of fatty alcohol sulphates obtained from natural fatty acids, alkaline or alkaline-earth metal salts of sulphuric or sulphonic acid esters (such as sodium lauryl sulphate) and sulphonic acids of fatty alcohol/ethylene oxide adducts. Examples of alkylarylsulphonates are the sodium, calcium or alcanolamine salts of dodecylbenzene sulphonic acid or dibutyl-naphtalenesulphonic acid or a naphtalene-sulphonic acid/formaldehyde condensation product. Also suitable are the corresponding phosphates, e.g. salts of phosphoric acid ester and an adduct of p-nonylphenol with ethylene and/or propylene oxide) and the like.

- The term " other excipient " as used herein refers to additives such as ureum, silicon, magnesium oxide, azo dyes, organic and inorganic pigments such as titanium dioxide, flavours, antioxidants, UV-absorbers, stabilisers, odour masking agents, viscosity enhancers and the like.
- The term " rate controlling polymer " as used herein refers e.g. to polymers such as poly(ethylene oxide), polyvinylalcohol, polyvinylacetate, poly (methylvinylether-co-maleic anhydride), polycaprolactone, poly(ethylene-co-vinylacetate), polyethylene,

polyvinylchloride, poly(ethylene-co-acrylic acid), polypropylene, polymethacrylic acid, poly-aminoacids, polyvinylpyrrolidone, carboxymethyl-cellulose, protamine sulfate and the like, and mixtures thereof .

According to this invention, the core component may be different from the outer layer component or (except when the core component consists of a lipophilic material) may belong to the same class of components as the layer component. A particular construction of the biologically active composite solid shaped article of the invention which proved to be especially and unexpectedly useful consists of selecting a starch component for the layer component and/or selecting a starch component or a lipophilic material for the core component. Furthermore, the outer layer and the inner core filling the said outer layer may comprise the same or different types of plasticizers, lubricants, rate controlling polymers and optionally other excipients.

The biologically active composite solid shaped article of this invention may have any shape such as cylindrical, ellipsoidal, tubular, sheet-like (for example for transdermal therapeutic applications) or similar, i.e. its section may be circular, elliptic, square, rectangular or the like. It may have any dimension usually suitable for the delivery of a biologically active ingredient for a specific agronomic or therapeutic application. For instance, when it is intended to be used for a pharmaceutical or veterinary application for administration to a human or an animal (e.g. a mammal), the inner core should preferably have a dimension from about 0.1 to 10 cm, more preferably from 0.1 to 1 cm, and/or the outer layer should preferably have a thickness from 0.1 to 5 cm, more preferably from 0.1 to 1 cm. The relative dimension of the outer layer (i.e. its thickness), with respect to the dimension of the inner core, is not critical to the present invention and may be higher or lower than or equal to the same.

The outer layer and the inner core (except when the core component is a lipophilic material) may both be produced by means of hot stage extrusion. They can either be made separately and then assembled manually or automatically, or preferably they can be made and assembled simultaneously into a composite solid shaped article by means of co-extrusion according to the first process such as described above in the summary of the invention.

Such first process may suitably be performed by means of conventional and commercial equipment known to those skilled in the art such as a co-rotating twin screw extruder with, for instance, the following dies:

- Cylindrical shape:

Cylindrical die: 0.1 cm to 10 cm

Tubular die: 0.1 cm to 5 cm (wall diameter)

- Laminated (sheet-like) shape:

Multiple sheet die: 1 cm to 50 cm (width) – 0.1 cm to 2 cm (height)

- Ellipsoidal shape:

Ellipsoidal die: 0.5 to 20 cm (width) – 0.1 to 10 cm (height)

Ellipsoidal pipe die: 0.1 to 5 cm (wall diameter).

The processing parameters such as pressure, temperature, feed rate of material, amounts and feed rates of water, plasticizer and other excipients in the production process of the invention are dependent on the type of biologically active ingredient or other component, the twin-extruder model used and other conditions, but it is important to select a combination of parameters such that the biologically active ingredient and/or other component will be maintained at temperatures below their decomposition points, and to vary the operating parameters according to the desired characteristics of the composite article.

The biologically active composite solid shaped article of this invention is suitable for the controlled release of a variety of biologically active ingredients (herein-above B and optionally A) such as therapeutic agents or drugs with different physicochemical characteristics and is therefore suitable for the manufacture of medicaments for various therapies such as anti-thrombotic, anti-inflammatory, anti-proliferative, anti-allergic or anti-microbial. It can therefore be used under various forms, such as an oral drug delivery system, as an implant (e.g. subcutaneous), as a transdermal sheet or for other drug delivery routes (such as vaginal, uterine, ocular, etc.) in humans (pharmaceutical applications) as well as in animals (veterinary applications). The release characteristics of the above-mentioned biologically active

ingredient B (and optionally A) in the composite solid shaped article of the invention can easily be modified namely by:

1) changing the composition of the outer layer and/or the inner core by altering the type or concentration of the layer component and/or the core component and/or the plasticizer and/or the lubricant and/or the rate controlling polymer or by adding other excipients,
2) changing the respective dimensions of the outer layer and/or the inner core,
3) loading the outer layer with (preferably a minor amount of) a biologically active ingredient.

The following examples are provided for illustrative purpose only, and should in no way be interpreted as limiting the scope of the present invention.

Dissolution profiles of a few biologically active composite articles of the invention are shown in the following examples (wherein the wall diameter of the outer layer die is 1 mm), which were performed in a manner similar to the comparative example shown in figure 1 herein-above. As can be concluded from figures 3 to 6, the biologically active composite solid shaped articles of this invention exhibit an essentially zero order drug release, without burst release effect, which is significantly slower than the drug release from the system that was tested *in vivo* by D. Henrist et al., *Int. J. Pharm.* (1999) 187, 185-191 (profile shown in figure 1).

EXAMPLE 1

In figure 3, the dissolution profile of a reference hot stage extrusion formulation (diameter 3 mm) consisting of 53% corn starch, 15% sorbitol, 2% glyceryl monostearate and 30% theophylline monohydrate ( ) was compared to the dissolution profiles of:

- a first composite solid shaped article comprising the above reference formulation as the inner core and an outer layer consisting of 15% sorbitol, 2% glyceryl monostearate and 83% corn starch ( ),
- a second composite solid shaped article similar to the previous one except for an outer layer consisting of 15% sorbitol, 2% glyceryl

monostearate, 78% corn starch and 5% theophylline monohydrate ( ), and

- a third composite solid shaped article similar to the previous one except for an outer layer consisting of 15% sorbitol, 2% glyceryl monostearate, 80.5% corn starch and 2.5% theophylline monohydrate (•).

EXAMPLE 2

In figure 4, the dissolution profile of a reference hot stage extrusion formulation (diameter 3 mm) consisting of 53% corn starch, 15% sorbitol, 2% glyceryl monostearate and 30% theophylline monohydrate ( ) was compared to the dissolution profiles of composite solid shaped articles with different inner core diameters: 1.5 mm (•), 3 mm (▲) and 5 mm (■). All inner cores consist of 53% corn starch, 15% sorbitol, 2% glyceryl monostearate and 30% theophylline monohydrate. All outer layers consist of 83% corn starch, 15% sorbitol and 2% glyceryl monostearate.

EXAMPLE 3

Figure 5 provides dissolution profiles of composite solid shaped articles with a different drug loading in the inner core: 30% theophylline monohydrate (◆) and 40% theophylline monohydrate (■). The outer layers consisted of 83% corn starch, 15% sorbitol and 2% glyceryl monostearate. The inner cores had a diameter of 5 mm and consisted of the above-mentioned drug amount, 15% sorbitol, 2% glyceryl monostearate and corn starch as complement to 100%.

EXAMPLE 4

In this embodiment, the mixture for the outer layer consisted of 83% corn starch, 15% sorbitol and 2% glyceryl monostearate and extrusion was performed with 20% water at 200 rpm, a total feed rate of 3 kg/h and a maximal temperature of 100°C. The layer was filled with an inner core comprising a mixture of molten triglycerides (Whitepsol® H15 (W)) and theophylline monohydrate(TM). After this lipophylic mixture was solidified within the inner core, dissolution was performed. Figure 6 provides dissolution

profiles of pipes filled with 90% W and 10% TM (◆), 80% W and 20% TM (■), and 70% W and 30% TM (▲).

EXAMPLE 5

In figure 7 the mean plasma concentration (C) – time (t) *in vivo* profile after administration of 300 mg theophylline in the form of a reference hot stage extrusion formulation F (I) consisting of 53% corn starch, 15% sorbitol, 30% theophylline monohydrate and 2% glyceryl monostearate was compared to the corresponding profiles after administration of 300 mg theophylline in the form of two different solid shaped composite articles of this invention:

- formulation F-1(II): outer layer consists of 15% sorbitol, 2% glyceryl monostearate, 2.5% theophylline monohydrate and 80.5% corn starch; inner core consists of 15% sorbitol, 2% glyceryl monostearate, 30% theophylline monohydrate and 53% corn starch.
- formulation F-2(II): outer layer consists of 15% sorbitol, 2% glyceryl monostearate and 83% corn starch; inner core consists of 15 % sorbitol, 2 % glyceryl monostearate, 30% theophylline monohydrate and 53% corn starch.

The following table presents the values of:

- t_{max} being the time at which C is maximum,
- C_{max} being the maximum concentration, and
- $t_{75\ \%\ Cmax}$ being the time span during which the plasma concentration is at least 75 % of the maximal plasma concentration.

Table

	t_{max} (h)	C_{max} ($\mu g.ml^{-1}$)	$t_{75\%Cmax}$ (h)
F-1(II)	9.3	5.1	8.5
F-2(II)	10.0	5.1	8.5
F(I)	4.6	6.3	5.4

Taking $t_{75\ \%\ Cmax}$ as a measure of the sustained release characteristic of a formulation, this clearly shows an unexpected improvement of the composite articles of the invention over the single matrix system of the prior art.

CLAIMS

1. A biologically active composite solid shaped article comprising:

(a) an outer layer comprising:

- at least one layer component selected from a starch component, a cellulose derivative and an acrylate (co)polymer, and
- optionally one or more additives selected from plasticizers for the said layer component, lubricants, rate controlling polymers and other excipients, and
- further optionally at least one biologically active ingredient A, and

(b) an inner core filling the said outer layer and comprising:

- at least a biologically active ingredient B,
- at least one core component selected from a starch component, a lipophilic material, a cellulose derivative and an acrylate (co)polymer, and
- optionally one or more additives selected from plasticizers for the said core component, lubricants, rate controlling polymers and other excipients.

2. A biologically active composite solid shaped article according to claim 1, characterized in that the outer layer comprises, per 100 parts by weight of the said layer:

- from 1 to 100 parts of at least one layer component,
- from 0 to 50 parts of one or more plasticizers for the said layer component,
- from 0 to 50 parts of one or more lubricants,
- from 0 to 50 parts of one or more rate controlling polymers,
- from 0 to 50 parts of one or more other excipients, and
- from 0 to 99 parts of the biologically active ingredient A.

3. A biologically active composite solid shaped article according to claim 1 or claim 2, characterized in that the inner core comprises, per 100 parts by weight of the said core:

- from 1 to 100 parts of at least one core component,

- from 0 to 50 parts of one or more plasticizers for the said core component,
- from 0 to 50 parts of one or more lubricants,
- from 0 to 50 parts of one or more rate controlling polymers,
- from 0 to 50 parts of one or more other excipients, and
- from 0 to 99 parts of at least a biologically active ingredient B.

4. A biologically active composite solid shaped article according to any of claims 1 to 3, characterized in that the layer component is a starch component.

5. A biologically active composite solid shaped article according to any of claims 1 to 4, characterized in that the core component is a starch component or a lipophilic material.

6. A process for making a biologically active composite solid shaped article, comprising:

(a) forming a mixture (A) comprising:

- at least one layer component selected from a starch component, a cellulose derivative and an acrylate (co)polymer, and
- optionally one or more additives selected from plasticizers for the said layer component, lubricants, rate controlling polymers and other excipients, and
- further optionally a biologically active ingredient A, and

wherein the said process further comprises:

(b) forming a mixture (B) comprising:

- at least a biologically active ingredient B,
- at least one core component selected from a starch component, a cellulose derivative and an acrylate (co)polymer, and
- optionally one or more additives selected from plasticizers for the said core component, lubricants, rate controlling polymers and other excipients, and

(c) co-extruding mixture (A) and mixture (B) at a temperature from 20 to 180°C

in order to form an outer layer from the extrudate of mixture (A) and an inner core filling the said outer layer from the extrudate of mixture (B), or

separately extruding mixture (A) and mixture (B) at a temperature from 20 to 180°C in order to form an outer layer from the extrudate of mixture (A) and an inner core from the extrudate of mixture (B) and further assembling both extrudates in such a manner that the inner core fills the outer layer,

or wherein the said process further comprises:

(d) extruding mixture (A) at a temperature from about 20 to 180°C in order to form an outer layer from the extrudate of mixture (A),

(e) forming a mixture (C) comprising:

- at least a biologically active ingredient B,
  lipophilic material as a core component, and
- optionally one or more additives selected from plasticizers for the said core component, lubricants, rate controlling polymers and other excipients,

and

(f) melt-homogenizing mixture (C) and filling the melt-homogenized mixture (C) into the outer layer during or after extrusion of mixture (A).

7. A biologically active product comprising a composite solid shaped article according to any of claims 1 to 5 or obtainable from the process of claim 6.

8. A biologically active product according to claim 7, in the form of a tablet or a gelule or an implant or a transdermal sheet.

9. A biologically active composite solid shaped article according to any of claims 1 to 5 or a biologically active product according to claim 7, wherein the biologically active ingredient A and/or the biologically active ingredient B is a therapeutic agent.

10. Use of a composite solid shaped article according to any of claims 1 to 5 or obtainable from the process of claim 6 or of a biologically active product according to claim 7 or claim 8 for the controlled delivery of a biologically active ingredient for agronomic or therapeutic application.

Figure 1

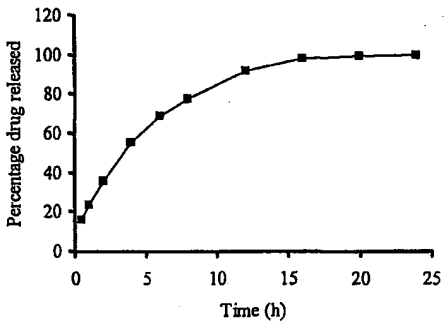


Figure 2

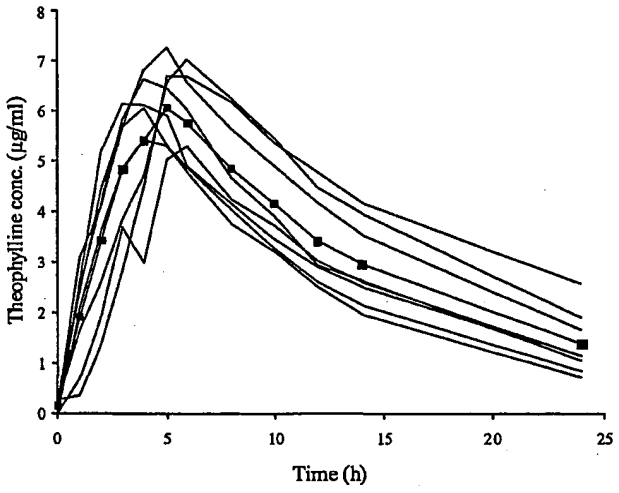
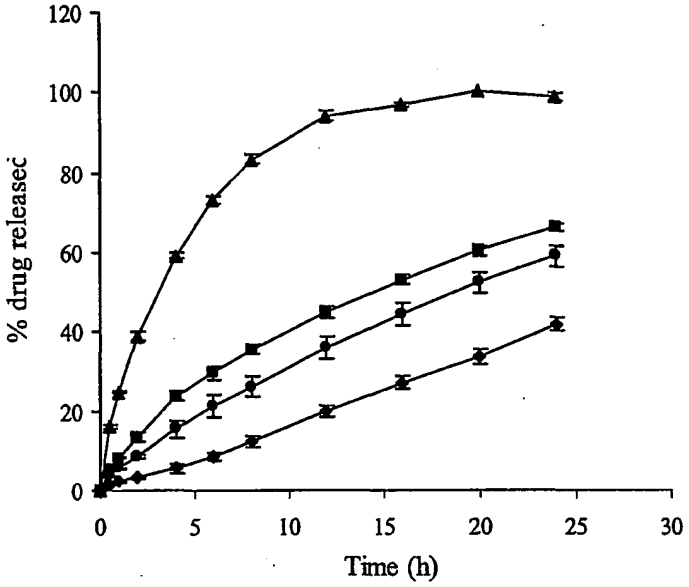


Figure 3



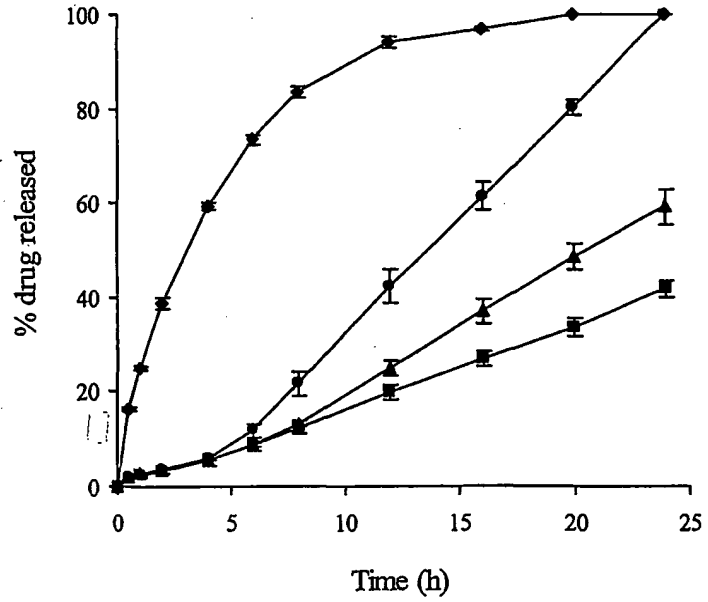


Figure 4

Figure 5

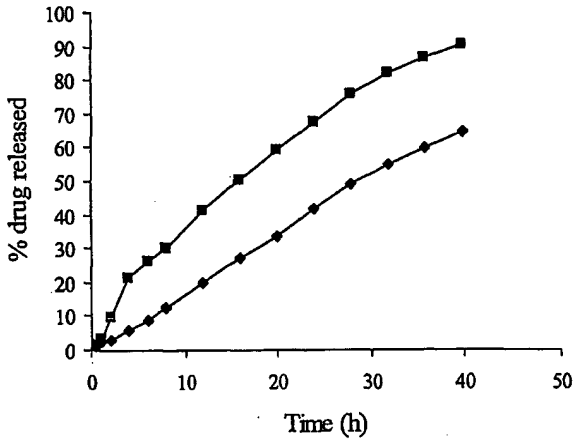


Figure 6

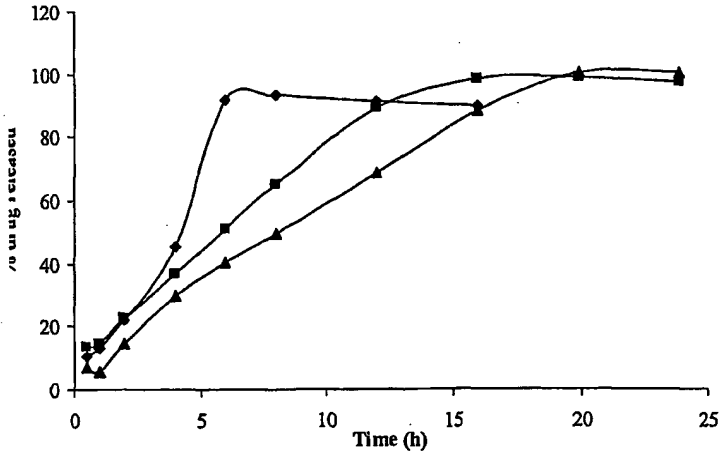


Figure 7

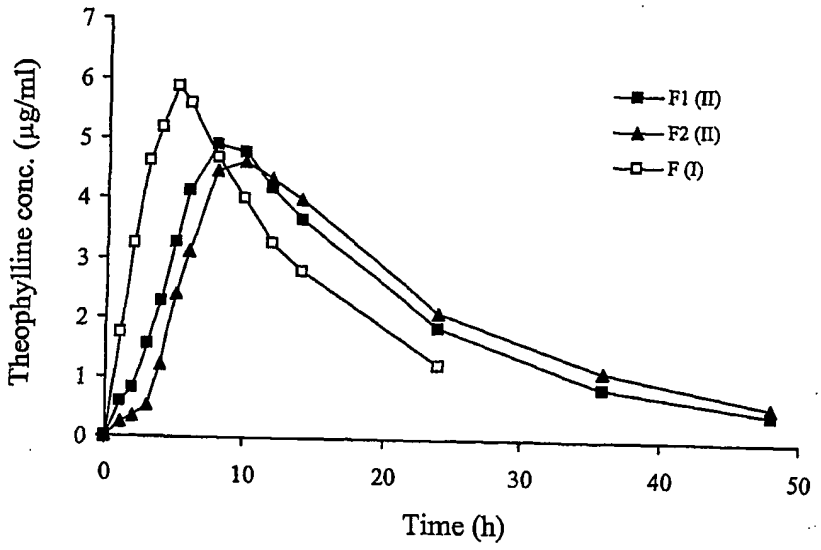
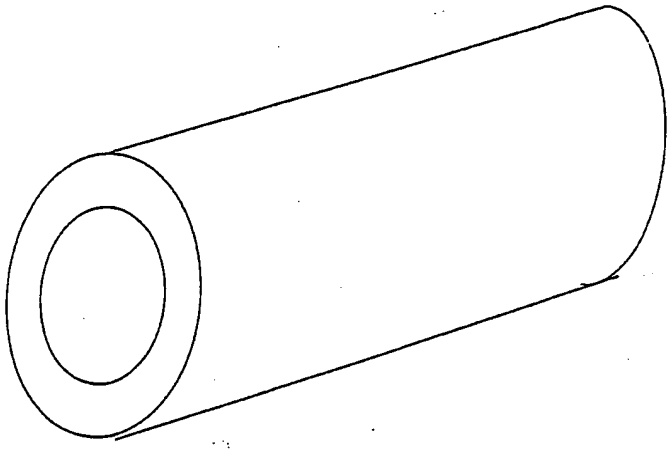

Theophylline conc. (µg/ml)
Time (h)
F1 (II)
F2 (II)
F (I)
0
1
2
3
4
5
6
7
0
10
20
30
40
50

Figure 8



INTERNATIONAL SEARCH REPORT

ational Application No
PCT/EP 01/08123

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/24 A61K9/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 December 2001	27/12/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Epskamp, S

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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